Systematic review of the influence of chemotherapy-associated liver injury on outcome after partial hepatectomy for colorectal liver metastases

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Background: **The impact of chemotherapy-associated liver injury (CALI) on postoperative outcome in patients undergoing partial hepatectomy for colorectal liver metastases (CRLM) remains controversial. The objective of this study was to clarify the effect of CALI (sinusoidal dilatation (SD), steatosis and steatohepatitis) on postoperative morbidity and mortality by investigating a large data set from multiple international centres.**

Methods: **PubMed and Embase were searched for studies published between 1 January 2004 and 31 December 2013 with keywords 'chemotherapy', 'liver resection', 'outcome' and 'colorectal metastases' to identify potential collaborating centres. Univariable and multivariable analyses were performed using binary logistic regression models, with results presented as odds ratios (ORs) with 95 per cent confidence intervals.**

Results: **A consolidated database comprising 788 patients who underwent hepatectomy for CRLM in eight centres was obtained. In multivariable analyses, severe SD was associated with increased major morbidity (Dindo–Clavien grade III–V; OR 1·73, 95 per cent c.i. 1·02 to 2·95; $P = 0·043$). Severe steatosis was associated with decreased liver surgery-specific complications (OR 0·52, 95 per cent c.i. 0·27 to 1·00; $P = 0·049$), whereas steatohepatitis was linked to an increase in these complications (OR 2·08, 1·18 to 3·66; $P = 0·012$). Subgroup analysis showed that lobular inflammation was the sole component associated with increased overall morbidity (OR 2·22, 1·48 to 3·34; $P = 0·001$) and liver surgery-specific complications (OR 3·35, 2·11 to 5·32; $P < 0·001$). Finally, oxaliplatin treatment was linked to severe SD (OR 2·74, 1·67 to 4·49; $P < 0·001$).**

Conclusion: **An increase in postoperative major morbidity and liver surgery-specific complications was observed after partial hepatectomy in patients with severe SD and steatohepatitis. Postoperative liver failure occurred more often in patients with severe SD.**

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Introduction

Colorectal cancer is the third most common cancer worldwide, affecting over 1·3 million patients annually[1]. Approximately 50 per cent of these patients develop colorectal liver metastases (CRLM)[2,3]. Although liver resection provides the best prospect of cure, only 10–30 per cent of patients with liver metastases are eligible for hepatic surgery[3,4]. For patients with tumours deemed unresectable, neoadjuvant systemic chemotherapy can prolong survival, and potentially allow future hepatic resection[2,5].

For decades, 5-fluorouracil (5-FU) was the sole option for treating CRLM. This has changed markedly in the new millennium; with the approval of irinotecan, oxaliplatin and humanized monoclonal antibodies, approximately 15 per cent of patients with initially unresectable tumours became eligible for liver resection[6,7]. Unfortunately, administration of irinotecan- and/or oxaliplatin-based chemotherapeutic agents has been associated with a harmful side-effect in the form of liver injury[8,9].

Chemotherapy-associated liver injury (CALI) is often reported in patients with CRLM, and appears to be regimen-specific. For instance, oxaliplatin treatment is associated with sinusoidal obstruction syndrome (SOS)[10], and linked to increased occurrence of nodular regenerative hyperplasia (NRH)[11]. Co-administration of bevacizumab with oxaliplatin, however, has been reported to be associated with a decrease in both the incidence and severity of SOS and NRH[10–12]. Irinotecan-based regimens appear to be related to the development of steatohepatitis[8,13,14]. Importantly, because patients commonly receive several chemotherapeutic agents to offer optimal benefit in downsizing tumours, it is difficult to identify the specific agents responsible for injury to the hepatic parenchyma.

Certain studies[9,13,15–18] have claimed a negative correlation between CALI and postoperative outcome (postoperative morbidity, mortality), but others[19–23] could not reproduce this. Therefore, it remains unclear whether CALI influences postoperative morbidity and mortality. The aim of the present study was to explore whether sinusoidal dilatation (SD), steatosis and steatohepatitis are associated with increased morbidity and mortality rates after partial hepatectomy by performing a meta-analysis of individual participant data based on a systematic literature review. Additionally, factors associated with the occurrence of CALI were identified.

Methods

An extensive protocol, written before the start of this study, can be found in *Appendix S1* (supporting information). PRISMA and MOOSE guidelines were followed when conducting and reporting this review[24,25].

Search strategy for identification of studies

Systematic searches were performed in MEDLINE (PubMed) and Embase for studies published between 1 January 2004 and 31 December 2013 using a search matrix including the following four categories: liver resection, chemotherapy, tumour type and outcome. For the purpose of performing a more comprehensive search, the type of liver injury was not included in the search matrix. The full search strategy is shown in *Table S1* (supporting information). The first publication date was fixed at 2004 because the widely used criteria for scoring SD, steatosis and steatohepatitis were developed in 2004[26] and 2005[27]. No language filter was applied.

Inclusion criteria

Studies meeting the following criteria were considered eligible for inclusion: adult patients (aged over 18 years), who underwent liver resection for CRLM, with description of postoperative short-term overall morbidity, liver surgery-specific complications, postoperative liver failure or overall mortality (within 90 days or in-hospital) after liver resection, and with pathological assessment of non-tumorous liver specimens for SD, steatosis and/or steatohepatitis (*Table S2*, supporting information). Studies with patients who received preoperative hepatic arterial infusion of chemotherapy were excluded, as were case reports, comments, those with published abstracts only, editorials and reviews.

Study identification and data collection

Duplicates were removed. Two authors independently screened all titles and abstracts and excluded those not pertinent to the review. Any discrepancy was resolved by consensus. The remaining articles were included for full-text revision and assessed independently for eligibility by the two authors. Reference lists of fully reviewed articles were checked manually for additional potential citations, along

with exploration of a personal library that was established during previous research on this topic[28,29].

Definitions

SD was graded according to Rubbia-Brandt and colleagues[26], with grade 2–3 (severe SD) considered clinically relevant as it reflects rupture of sinusoidal wall integrity. SD is one of the most important histological features of SOS, and its severity is generally accepted to correspond to the severity of SOS. Steatosis and steatohepatitis were graded according to the system of Kleiner *et al.*[27]. Severe steatosis was defined as more than 33 per cent of parenchyma affected by steatosis[27]. A non-alcoholic steatohepatitis activity score (NAS) of 4 or more was considered as steatohepatitis to provide a working cut-off value conforming with the literature[30]. CALI was defined as any occurrence of severe SD, severe steatosis or steatohepatitis. Comorbidity was defined as any disease affecting the patient apart from CRLM (diabetes mellitus, pulmonary, renal, cardiovascular and other diseases). Overall morbidity was defined as any complication occurring within 90 days after surgery or during the hospital stay, and graded according to the classification of Dindo and colleagues[31]. Major morbidity was defined as Dindo–Clavien grade III (requiring invasive intervention) or higher. The concept of a liver surgery-specific complication was analogous to the liver surgery-specific composite endpoint developed in 2011, and included one or more of the following events: ascites, postoperative liver failure, bile leakage, intra-abdominal abscess, intra-abdominal haemorrhage and operative mortality[32]. Postoperative liver failure was defined as the concurrent presence of a prothrombin time below 50 per cent and a serum bilirubin level greater than 50 μmol/l (the 50–50 criteria) on or after postoperative day 5[33]. Postoperative mortality included death from any cause within 90 days after surgery or during the hospital admission. Major hepatectomy was defined as resection of three or more Couinaud liver segments[34].

Risk-of-bias assessment

The risk of bias of the final included studies was assessed independently by two blinded researchers using the Quality in Prognosis Studies (QUIPS) tool[35,36]. Discrepancies were discussed by the two authors and consensus was reached. The QUIPS tool includes six bias domains: participation, attrition, prognostic factor measurement, confounding measurement and account, outcome measurement, and analysis and reporting. The results of assessment of each of the six domains were taken together to calculate an overall low, moderate or high risk of bias, as follows: overall low risk of bias, two or fewer domains rated as moderate risk and the remaining domains as low risk; overall moderate risk, at least three domains rated as moderate risk and the remaining domains as low risk; and high overall risk, one or more domains rated as high risk, independent of the rating of the remaining domains.

Data handling and statistical analysis

Corresponding authors from studies that fulfilled the inclusion criteria were contacted by e-mail for collaboration and sharing of coded data (by numbering) for the published cohort. Each author was asked to sign a specific data transfer agreement form, which assured careful handling of the data. Coded data were arranged in a preconstructed Excel™ file (Microsoft, Redmond, Washington, USA) and subsequently imported into SPSS® for Windows® version 20.0 (IBM, Armonk, New York, USA).

Patient characteristics were compared using the Student's *t* test for numerical variables. For categorical variables, the Pearson χ^2 test with continuity correction was applied, or Fisher's exact test when any of the expected values was smaller than five. The influence of preoperative chemotherapeutic agents on liver injury, and subsequently the effect of liver injury on short-term postoperative outcome, were analysed by applying one-step binary logistic regression models. Individual participant data from all studies were pooled and modelled simultaneously. This approach was considered more optimal because each study showed relatively few events per outcome and small sample sizes, and the one-step approach for pooled data allowed the exact binomial distribution to be used and did not require continuity corrections when there were no events[37,38]. For missing values, multiple imputations were performed, assuming that data were missing at random. The number of imputations was determined by the maximum percentage of missing data in the data set. In this study, 30 imputations were performed, as the maximum amount of missing data was 26 per cent (minor/major morbidity). Variables in multiple imputations are listed in *Table S3* (supporting information). A complete-case sensitivity analysis was also conducted. Clustering of patients from different studies was integrated as a separate co-variable ('database source') and included in binary logistic regression models in every analysis[38]. A single variable together with database source created the univariable model. All variables with $P \leq 0{\cdot}200$ in univariable analysis were included in the multivariable analysis. In addition, database source and variables known to be related to the outcome (either well described in literature or based on

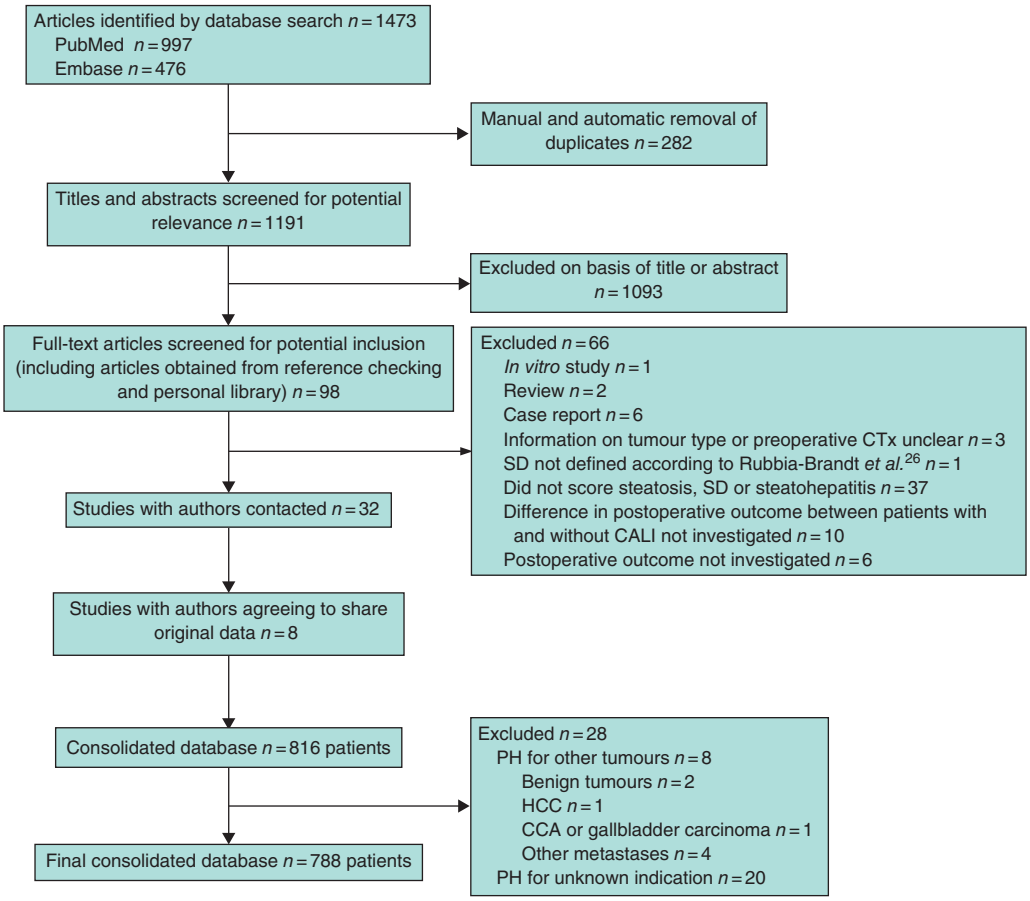

Fig. 1 Flow chart showing selection of articles for review. CTx, chemotherapy; SD, sinusoidal dilatation; CALI, chemotherapy-associated liver injury; PH, partial hepatectomy; HCC, hepatocellular carcinoma; CCA, cholangiocarcinoma

careful discussion and consensus between the authors) were forced into the multivariable model.

A subgroup analysis including only patients who received oxaliplatin-based treatment was performed to investigate the impact of bevacizumab on the occurrence of severe SD. At a later stage of the study, data to investigate the influence of separate NAS subcategories (steatosis, lobular inflammation and hepatocellular ballooning) on postoperative outcome were requested. A subgroup analysis including cohorts with available data on NAS subcategories was undertaken. The methods of analysis of these data were identical to those described above. Unadjusted and adjusted odds ratios (ORs) with 95 per cent confidence intervals were calculated. $P \leq 0{\cdot}050$ was considered significant for all analyses.

Results

The search strategy resulted in 1191 unique hits (*Fig. 1*). In total, 1093 articles were excluded on the basis of title or abstract, and the remaining 98 articles were subjected to full-text evaluation. Thirty-two studies met the inclusion criteria and the 30 corresponding authors were contacted by e-mail. Nineteen responded, of whom eight agreed to share their raw data. Other authors could not be contacted (*Fig. S1*, supporting information). Potential publication bias was excluded by testing for asymmetry in a funnel plot. The eight included studies[16,17,39–44] were assessed for risk of bias using the QUIPS tool. Overall ratings are shown in *Table 1*. Six articles showed an overall low risk of bias and one study each had a moderate or high risk. Detailed scoring can be found in *Table S4* (supporting information). Because the individual participant data from all studies were pooled and modelled simultaneously, an overall rating was also calculated without taking the study confounding and statistical analysis domains into account; all studies then showed a low risk of bias based on the remaining four domains.

Characteristics of the included studies are summarized in *Table 1*. The consolidated cohort consisted of 816 patients

Table 1 Characteristics of studies included in final database

Reference	Country	Study type	Population*	QUIPS score	Comparisons	Key findings
Gómez-Ramírez *et al.*[39]	Spain	PCS	45 (46)	Low	Neoadjuvant CTx *versus* no CTx	Patients treated with oxaliplatin had a higher incidence of SOS, an increase in liver complications and longer mean hospital stay
Nam *et al.*[40]	Korea	RCS	89	Low	Oxaliplatin CTx *versus* non-oxaliplatin CTx	Sinusoidal injury is frequently seen in oxaliplatin-treated livers and should be documented in surgical pathology practice when extensive
Pessaux *et al.*[41]	France	RCC	52 (36)	High	Neoadjuvant CTx *versus* CTx + cetuximab/bevacizumab	The addition of bevacizumab or cetuximab to the neoadjuvant CTx does not increase morbidity rates after hepatectomy for CRLM
Pilgrim *et al.*[16]	Australia	RCS	232	Low	Severe *versus* non-severe CALI	Severe steatosis was associated with increased postoperative morbidity, whereas severe steatohepatitis and sinusoidal injury were not
Soubrane *et al.*[42]	France	RCS	78 (105)	Low	Severe *versus* non-severe SD	SOS 2–3 was associated with postoperative hepatic dysfunction and ascites after major liver resection
Takamoto *et al.*[43]	Japan	RCS	55 (104)	Moderate	Liver injury *versus* no liver injury	Hepatic functional reserve, represented by the ICG-R15 value, improves during the period after cessation of chemotherapy
van der Pool *et al.*[44]	The Netherlands	RCS	104	Low	Neoadjuvant CTx *versus* CTx + bevacizumab	Bevacizumab added to oxaliplatin-based CTx may protect against moderate SD without significantly influencing morbidity
Viganò *et al.*[17]	Italy	PCS	100	Low	Severe *versus* non-severe CALI	Liver biopsy cannot be considered a reliable tool in assessing CALI except for steatosis. Proportion of liver dysfunction was higher among patients with CALI

*Values are number of patients in cohort reported in published article, with number in shared database in parentheses. QUIPS, Quality in Prognosis Studies; PCS, prospective cohort study; CTx, chemotherapy; SOS, sinusoidal obstruction syndrome; RCS, retrospective cohort study; RCC, retrospective case–control study; CRLM, colorectal liver metastases; CALI, chemotherapy-associated liver injury; SD, sinusoidal dilatation; ICG-R15, indocyanine green retention rate at 15 min.

(*Fig. 1*). Twenty-eight patients were excluded because they underwent surgery for indications other than CRLM, leaving 788 patients for analysis. Patient characteristics, surgical details and postoperative outcomes of the consolidated cohort are shown in *Table 2*. There were 453 men (57·5 per cent) and 335 women (42·5 per cent), with a median age of 61 (range 25–86) years. SD was severe in 183 patients (24·1 per cent), steatosis was severe in 117 (15·6 per cent) and steatohepatitis in 100 (14·5 per cent). Of the 525 patients who received 5-FU, 396 (75·4 per cent) had simultaneous treatment with oxaliplatin and 135 (25·7 per cent) with irinotecan. Of the 136 patients who received capecitabine, 119 (87·5 per cent) had simultaneous treatment with oxaliplatin. Cetuximab and bevacizumab were most frequently administered together with oxaliplatin. All 61 patients who received cetuximab, and 138 of 164 (84·1 per cent) who received bevacizumab, were co-treated with oxaliplatin. Of 635 patients with NAS subcategory data, 96 (15·1 per cent) had a NAS of 4 or more. Only three patients (3 per cent) with a NAS of 4 or higher did not show lobular inflammation. The relationship between NAS and lobular inflammation is summarized in *Table S5* (supporting information).

Sensitivity analysis showed similar results for complete-case analysis and that with multiple imputation (detailed information available on request). The influence of severe SD, severe steatosis, steatohepatitis and other potential factors related to short-term overall morbidity, liver

Table 2 Patient, surgical and postoperative characteristics

		Sinusoidal dilatation ($n = 760$)			Steatosis ($n = 752$)			Steatohepatitis ($n = 690$)		
	n	Non-severe ($n = 577$)	Severe ($n = 183$)	P†	Non-severe ($n = 635$)	Severe ($n = 117$)	P	NAS < 4 ($n = 590$)	NAS ≥ 4 ($n = 100$)	P†
Age (years)*	788	61(11)	60(10)	0·576‡	61(11)	60(9)	0·527‡	61(11)	61(10)	0·784‡
Sex				0·836			1·000			0·784
M	453	335 (58·1)	104 (56·8)		366 (57·6)	68 (58·1)		336 (56·9)	59 (59·0)	
F	335	242 (41·9)	79 (43·2)		269 (42·4)	49 (41·9)		254 (43·1)	41 (41·0)	
BMI (kg/m^2)*	706	25·3(4·4)	24·4(3·9)	0·001‡	24·7(4·1)	27·6(4·1)	< 0·001‡	24·9(4·2)	26·7(3·9)	< 0·001‡
Co-morbidity				0·259			0·012			0·158
No	363	247 (49·3)	93 (54·7)		290 (52·2)	41 (38·3)		271 (51·4)	31 (42)	
Yes	336	254 (50·7)	77 (45·3)		266 (47·8)	66 (61·7)		256 (48·6)	43 (58)	
Preoperative chemotherapy				0·001			0·032			0·198
No	127	110 (19·3)	15 (8·4)		114 (18·2)	11 (9·6)		112 (19·3)	13 (13)	
Yes	649	459 (80·7)	164 (91·6)		511 (81·8)	104 (90·4)		468 (80·7)	85 (87)	
5-FU				0·006			0·463			0·396
No	245	201 (35·6)	43 (24·2)		210 (34·0)	34 (29·8)		213 (37·0)	31 (32)	
Yes	525	363 (64·4)	135 (75·8)		408 (66·0)	80 (70·2)		362 (63·0)	66 (68)	
Capecitabine				0·173			0·158			0·061
No	634	454 (80·5)	152 (85·4)		511 (82·4)	87 (76·3)		466 (81·0)	70 (72)	
Yes	136	110 (19·5)	26 (14·6)		109 (17·6)	27 (23·7)		109 (19·0)	27 (28)	
Irinotecan				0·033			0·033			1·000
No	627	445 (78·9)	154 (86·5)		508 (81·9)	83 (72·8)		453 (78·8)	77 (79)	
Yes	143	119 (21·1)	24 (13·5)		112 (18·1)	31 (27·2)		122 (21·2)	20 (21)	
Bevacizumab				0·072			0·143			0·101
No	605	430 (76·4)	148 (83·1)		487 (78·7)	82 (71·9)		444 (77·4)	67 (69)	
Yes	164	133 (23·6)	30 (16·9)		132 (21·3)	32 (28·1)		130 (22·6)	30 (31)	
Cetuximab				0·198			0·716			0·462
No	708	522 (92·7)	159 (89·3)		566 (91·4)	106 (93·0)		522 (90·9)	91 (94)	
Yes	61	41 (7·3)	19 (10·7)		53 (8·6)	8 (7·0)		52 (9·1)	6 (6)	
Oxaliplatin				< 0·001			0·716			0·295
No	266	228 (40·5)	37 (20·8)		226 (36·5)	39 (34·2)		231 (40·2)	33 (34)	
Yes	503	335 (59·5)	141 (79·2)		393 (63·5)	75 (65·8)		343 (59·8)	64 (66)	
Resection type				< 0·001			0·921			0·713
Minor (< 3 segments)	398	330 (57·2)	67 (36·8)		335 (52·8)	63 (53·8)		339 (57·6)	55 (55·0)	
Major (≥ 3 segments)	389	247 (42·8)	115 (63·2)		299 (47·2)	54 (46·2)		250 (42·4)	45 (45·0)	
PVE				0·001			0·046			0·512
No	623	461 (92·0)	140 (82·4)		498 (89·6)	103 (96·3)		491 (93·2)	71 (96)	
Yes	76	40 (8·0)	30 (17·6)		58 (10·4)	4 (3·7)		36 (6·8)	3 (4)	
Pringle manoeuvre				0·018			0·974			1·000
No	446	347 (64·5)	93 (54·1)		366 (62·1)	71 (62·8)		349 (63·9)	61 (64)	
Yes	291	191 (35·5)	79 (45·9)		223 (37·9)	42 (37·2)		197 (36·1)	34 (36)	
Transfusion of packed RBCs				0·004			0·871			0·382
No	646	492 (86·2)	139 (76·8)		529 (84·4)	100 (85·5)		508 (86·8)	83 (83·0)	
Yes	134	79 (13·8)	42 (23·2)		98 (15·6)	17 (14·5)		77 (13·2)	17 (17·0)	
Postoperative short-term outcomes										
Length of hospital stay (days)*	768	14(13)	15(11)	0·240‡	15(11)	14(17)	0·660‡	14(12)	15(14)	0·266‡
Overall morbidity				0·009			0·935			0·024
No	443	339 (59·3)	87 (47·8)		360 (57·3)	66 (56·4)		355 (60·6)	48 (48·0)	
Yes	338	233 (40·7)	95 (52·2)		268 (42·7)	51 (43·6)		231 (39·4)	52 (52·0)	
None/minor morbidity (DC 0–II)	491	362 (88·5)	106 (73·1)	< 0·001	397 (85·6)	69 (85)	1·000	367 (89·5)	62 (81)	0·041
Major morbidity (DC III–V)	89	47 (11·5)	39 (26·9)		67 (14·4)	12 (15)		43 (10·5)	15 (19)	
Liver surgery-specific complication				< 0·001			0·031			0·247
No	598	455 (79·8)	121 (66·9)		475 (75·9)	100 (85·5)		470 (80·6)	75 (75·0)	
Yes	180	115 (20·2)	60 (33·1)		151 (24·1)	17 (14·5)		113 (19·4)	25 (25·0)	
Mortality				0·200§			1·000§			0·422§
No	780	573 (99·3)	179 (97·8)		628 (98·9)	116 (99·1)		586 (99·3)	98 (98·0)	
Yes	8	4 (0·7)	4 (2·2)		7 (1·1)	1 (0·9)		4 (0·7)	2 (2·0)	
Postoperative liver failure				< 0·001			0·302§			1·000§
No	755	563 (98·6)	166 (91·7)		608 (97·0)	116 (99·1)		578 (99·0)	99 (99·0)	
Yes	24	8 (1·4)	15 (8·3)		19 (3·0)	1 (0·9)		6 (1·0)	1 (1·0)	

Value in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). Data represent original data without multiple imputations; owing to missing values, some numbers do not add up to the total number of patients. NAS, non-alcoholic fatty liver disease activity score; 5-FU, 5-fluorouracil; PVE, portal vein embolization; RBC, red blood cell; DC, Dindo–Clavien grade. †Pearson χ^2 test with continuity correction, except ‡Student's t test and §Fisher's exact test.

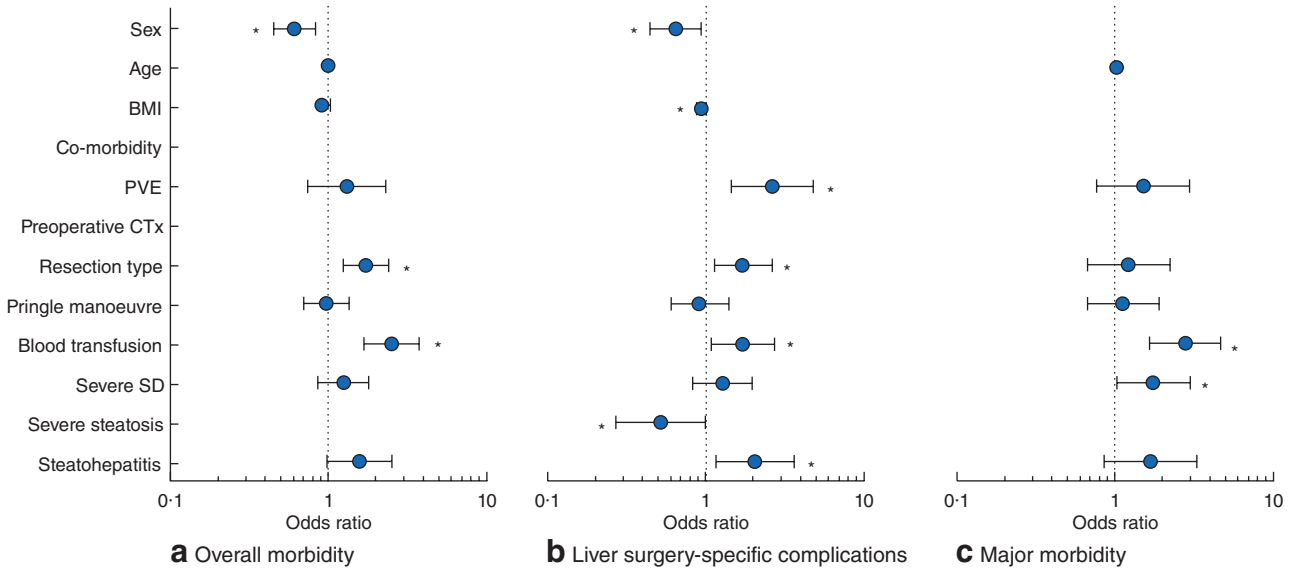

Fig. 2 Multivariable analysis of influence of liver injury on short-term postoperative outcomes: **a** overall morbidity, **b** liver surgery-specific complications and **c** major morbidity. Odds ratios are shown with 95 per cent confidence intervals. PVE, portal vein embolization; CTx, chemotherapy; SD, sinusoidal dilatation. *$P < 0{\cdot}050$

Table 3 Univariable analyses of factors influencing short-term postoperative outcome

	Postoperative liver failure ($n = 24$)		Mortality ($n = 8$)	
	Odds ratio	*P*	Odds ratio	*P*
Sex (F)	0·65 (0·25, 1·68)	0·376	0·50 (0·10, 2·25)	0·408
Age (years)	1·00 (0·96, 1·04)	0·937	1·03 (0·96, 1·05)	0·402
BMI (kg/m^2)	0·90 (0·80, 1·01)	0·070	0·96 (0·80, 1·14)	0·630
Co-morbidity	1·28 (0·53, 3·13)	0·583	7·84 (0·92, 66·65)	0·059
PVE	2·62 (0·95, 7·26)	0·064	1·09 (0·13, 9·09)	0·938
Preoperative chemotherapy	2·41 (0·30, 19·32)	0·409	1·51 (0·52, 4·42)	0·702
Resection type (major)	–*	–*	6·56 (0·77, 55·90)	0·085
Pringle manoeuvre	1·45 (0·57, 3·72)	0·437	1·91 (0·43, 8·54)	0·399
Blood transfusion	4·47 (1·69, 11·82)	0·003	14·00 (2·74, 71·51)	0·002
Severe SD	3·06 (1·18, 7·92)	0·021	2·79 (0·68, 11·44)	0·155
Severe steatosis	0·47 (0·06, 3·77)	0·473	0·86 (0·10, 7·09)	0·887
Steatohepatitis	1·90 (0·31, 22·83)	0·492	2·71 (0·57, 12·87)	0·210

Values in parentheses are 95 per cent confidence intervals. PVE, portal vein embolization; SD, sinusoidal dilatation. Multiple imputations were used for univariable analysis. *All patients with liver failure underwent major hepatectomy and none had minor hepatectomy ($P < 0{\cdot}001$, Fisher's exact test).

surgery-specific complications and major morbidity is shown in *Fig. 2* and *Table S6* (supporting information). Severe SD was significantly associated with increased major morbidity only (OR 1·73, 95 per cent c.i. 1·02 to 2·95; $P = 0{\cdot}043$). Severe steatosis was not significantly associated with the occurrence of postoperative overall or major morbidity, but was related to a decreased occurrence of liver surgery-specific complications (OR 0·52, 0·27 to 1·00; $P = 0{\cdot}049$). In contrast, patients with steatohepatitis showed a significantly increased rate of postoperative liver surgery-specific complications (OR 2·08, 1·18 to 3·66; $P = 0{\cdot}012$), and a trend towards increased overall morbidity (OR 1·58, 0·99 to 2·52; $P = 0{\cdot}057$).

Table 3 summarizes the effects of several factors associated with postoperative liver failure and mortality. Because of the small number of events, multivariable logistic regression was not performed. Postoperative liver failure occurred in 24 of 779 patients (3·1 per cent) in the study cohort (*Table 2*), seven women and 17 men, with a median age of 61 (range 48–75) years. All patients with liver failure had undergone major hepatectomy. The only factors strongly associated with increased liver failure in univariable analysis were severe SD (OR 3·06, 1·18 to

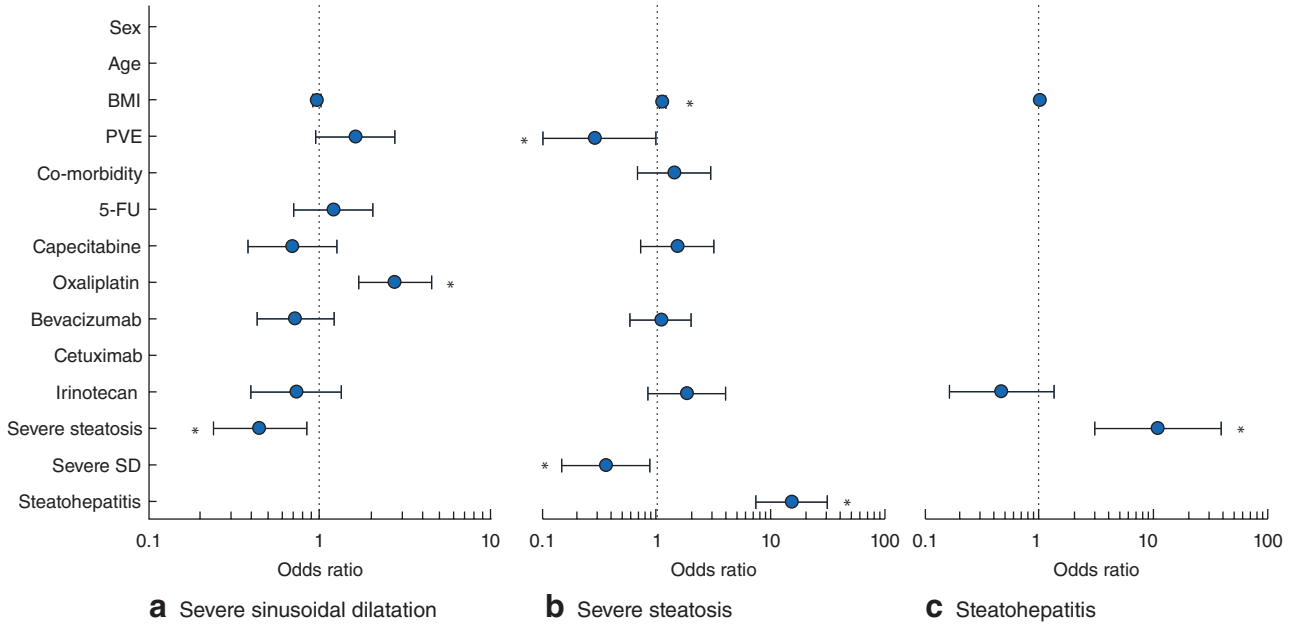

Fig. 3 Multivariable analysis of influence of risk factors on liver injury: **a** severe sinusoidal dilatation, **b** severe steatosis and **c** steatohepatitis. Odds ratios are shown with 95 per cent confidence intervals. PVE, portal vein embolization; 5-FU, 5-fluorouracil. *$P < 0{\cdot}050$

7·92; $P = 0{\cdot}021$) and perioperative blood transfusion (OR 4·47, 1·69 to 11·82; $P = 0{\cdot}003$).

In total, eight patients (1·0 per cent) died in the perioperative period after liver resection, seven within 90 days and one at 101 days during the hospital stay. The six men and two women had a median age of 64 (range 48–75) years. Perioperative blood transfusion (OR 14·00, 2·74 to 71·51; $P = 0{\cdot}002$) was the sole factor related to increased mortality in univariable analysis. A trend was found for major liver resection (OR 6·56, 0·77 to 55·90; $P = 0{\cdot}085$) and preoperative co-morbidity (OR 7·84, 0·92 to 66·65; $P = 0{\cdot}059$) to be associated with increased postoperative mortality. Severe SD (OR 2·79, 0·68 to 11·44; $P = 0{\cdot}155$), severe steatosis (OR 0·86, 0·10 to 7·09; $P = 0{\cdot}887$) and steatohepatitis (OR 2·71, 0·57 to 12·87; $P = 0{\cdot}210$) were not related to postoperative mortality.

Because steatohepatitis, but not severe steatosis, negatively affected postoperative short-term outcomes, lobular inflammation and hepatocellular ballooning were considered key factors for poor outcome. A subgroup analysis supported this hypothesis. In multivariable analyses, severe (grade 2–3) lobular inflammation was associated with increased overall postoperative morbidity (OR 2·22, 1·48 to 3·34; $P = 0{\cdot}001$) and liver surgery-specific morbidity (OR 3·35, 2·11 to 5·32; $P < 0{\cdot}001$), but not major morbidity (OR 1·63, 0·85 to 3·10; $P = 0{\cdot}138$). In contrast, neither severe steatosis (over 33 per cent) nor the presence of hepatocellular ballooning (grade 1–2) was associated with an increased complication rate in all multivariable analyses.

Associations between several preoperative variables and the occurrence of severe SD, severe steatosis and steatohepatitis are summarized in *Fig. 3* and *Table S7* (supporting information). Oxaliplatin (OR 2·74, 1·67 to 4·49; $P < 0{\cdot}001$) was related to increased occurrence of severe SD in multivariable analysis, whereas the addition of bevacizumab was associated with a twofold decrease in severe SD in patients who received oxaliplatin (OR 0·50, 0·30 to 0·82; $P = 0{\cdot}006$) when the analysis was adjusted solely by database source. Patients with severe steatosis showed a decreased incidence of severe SD (OR 0·44, 0·24 to 0·83; $P = 0{\cdot}011$) and *vice versa* (OR 0·36, 0·15 to 0·88; $P = 0{\cdot}025$). BMI was related to an increase in severe steatosis (OR 1·15, 1·08 to 1·21; $P < 0{\cdot}001$), whereas the incidence of severe steatosis was decreased in patients with portal vein embolization (PVE) (OR 0·29, 0·08 to 1·00; $P = 0{\cdot}050$). Only severe steatosis was significantly associated with an increased occurrence of steatohepatitis (OR 15·09, 6·25 to 36·45; $P < 0{\cdot}001$).

Discussion

In this study, an increase in postoperative major morbidity and liver surgery-specific complications after partial

hepatectomy was observed in patients with severe SD and steatohepatitis respectively, whereas severe steatosis was associated with a decreased occurrence of liver surgery-specific complications. Postoperative liver failure occurred more often in patients with severe SD. With respect to steatohepatitis, lobular inflammation, but not severe steatosis or hepatocellular ballooning, was strongly linked to increased postoperative morbidity. Oxaliplatin-based chemotherapy was independently associated with an increase in the occurrence of severe SD, whereas a decrease was seen with the addition of bevacizumab. An inverse relationship was found between severe SD and severe steatosis.

Mechanisms underlying the negative influence of severe SD on major morbidity are unknown, although preoperative hepatic dysfunction, impairment of liver regeneration, Kupffer cell dysfunction, enhanced blood loss due to haemorrhagic pools, fragility of the liver, and increased hepatocellular necrosis as seen in human and animal models, can all be reasons for poor liver function and an increased complication rate after severe SD[45,46]. However, as the *P* value was of borderline significance, the effect of severe SD on major morbidity must be interpreted with caution.

The progression of steatohepatitis is estimated by the so-called NAS, which is composed of scores for steatosis, lobular inflammation and hepatocellular ballooning[27]. Multivariable subgroup analyses examining the influence of these separate NAS subcategories on postoperative outcome showed a detrimental influence of lobular inflammation on all outcomes, whereas severe steatosis and hepatocellular ballooning had no effect. The mechanism behind steatohepatitis being a determinant of postoperative short-term outcomes is uncertain. Electron microscopy revealed that mitochondrial structural defects in hepatocytes correlate with steatohepatitis, but not with steatosis[47]. Moreover, the ability of the liver to recover from adenosine 5′-triphosphate depletion was severely impaired[48], liver regeneration was diminished[49], and humoral and cellular immune responses to enhanced oxidative stress were found in patients with steatohepatitis. These factors may account for postoperative complications.

Severe steatosis did not significantly influence short-term overall morbidity, major morbidity or mortality after partial hepatectomy in this study, which is in line with previous reports[50,51], but in contrast to findings in other studies[52,53]. Patients with severe steatosis even showed a decreased occurrence of liver surgery-specific complications. This might be explained by surgeons being more careful during surgery when observing a severely steatotic ('yellow') liver. However, with a *P* value of 0·049, this evidence needs to be validated by future research.

Severe SD was more common in patients who received oxaliplatin than among those who did not (29·6 *versus* 14·0 per cent). This is in line with previous studies[10,17] that showed a similarly high rate of severe SD after oxaliplatin-based regimens. The addition of bevacizumab, an angiogenesis inhibitor, to oxaliplatin-based chemotherapy has been associated with a decreased incidence of SD[44]. Indeed, when the analysis was restricted to the population that received oxaliplatin-based treatment, bevacizumab was associated with a greatly decreased occurrence of severe SD. Although mechanisms underpinning those observations remain unclear, activation of vascular endothelial growth factor and coagulation pathways in oxaliplatin-related SD might be involved[54].

Importantly, severe steatosis was linked to a decreased occurrence of severe SD and *vice versa*, raising the possibility that these events are mutually exclusive. Several phenomena could underlie this observation. First, mechanical pressure exerted by fat-laden, swollen hepatocytes may distort the hepatic microvasculature. In mice with severe steatosis, a decrease in sinusoidal perfusion, loss of fenestrae and narrowing of the sinusoidal lumen were observed[55]. SD may therefore not develop owing to spatial constraints. Conversely, atrophied hepatocellular plates in severe SD may render these hepatocytes incapable of fatty acid uptake. Alternatively, histological assessment may be more challenging in a liver affected by both severe SD and steatosis, increasing the likelihood of misclassification of either one of these injury types. However, several pathologists with hepatobiliary expertise independently considered this probability very small. Although the reduction in SD in patients with severe steatosis is interesting, central pathology review is needed to verify this finding.

Apart from oxaliplatin, preoperative PVE was marginally associated with an increased occurrence of severe SD. A previous study[56] has already acknowledged a possible influence of PVE on the development of vascular injury, probably by induction of ischaemia. The present authors hypothesize that the hepatic artery buffer response after PVE might play an even more profound role, as shown by the induction of microvascular remodelling and SD in the embolized lobe after portal branch ligation in a rodent model[57]. However, the morphology of the non-embolized remnant lobe may differ from that of the resected lobe, and liver histology and function may therefore not be affected after resection[58].

In the present study, severe SD was less common in patients receiving additional bevacizumab than among those receiving oxaliplatin alone. Severe SD was shown to be associated with an increased major complication rate and *vice versa*. Although the effect of co-administration of

oxaliplatin with bevacizumab on surgical outcome could not be investigated directly here, adding bevacizumab might provide an advantageous effect on postoperative outcome in patients treated with oxaliplatin.

Parenchymal damage due to chemotherapy can be diagnosed before surgery by radiological and biochemical means, as reviewed recently in detail[59]. Despite (experimental) research focusing on CALI, little evidence is available for its treatment in the human setting[59]. When liver injury is confirmed before operation, surgeons are thus advised to adapt surgical management to prevent complications. In the present study, the transfusion of packed red blood cells was associated with an increased postoperative complication rate, in line with previous literature[60]. Central venous pressure should be low during surgery to prevent excessive blood loss. Moreover, major hepatectomy was confirmed to be associated with an increased postoperative complication rate, which encourages minimization of the resection volume. Performing wedge resections instead of hemihepatectomy, and the use of radiofrequency ablation might be beneficial when feasible.

This study demonstrated both the effect of chemotherapy on liver injury and the subsequent effect of liver injury on short-term postoperative outcome in a large multicentre patient cohort. However, some limitations of the study should be discussed. First, NRH has recently caused concern because of its relationship to increased postoperative morbidity[11]. Although analysis of the effect of NRH on postoperative outcome would have been of interest, this was not possible owing to lack of available data. This may be because the data used in this review were from studies published before or around 2013, when NRH had not yet gained the attention it deserves. Inclusion of NRH is recommended when exploring the relationship between CALI and postoperative outcomes in future studies. Next, data on the interval between cessation of chemotherapy and partial hepatectomy, as well as the number of cycles administered, were not available for every study cohort. Therefore, the influence of these factors on the occurrence of CALI and short-term complications could not be evaluated. In addition, central review of all histopathology slides would have strengthened the paper substantially. Unfortunately, this was not feasible for logistical reasons. It must be highlighted, nonetheless, that all sections were reviewed by local pathologists with hepatobiliary expertise, and assessed according to uniform, well established and globally accepted scoring systems for SD, steatosis and steatohepatitis. Finally, as no RCTs exist on the topic, mainly retrospective cohort studies were included in this review. Despite this limitation, all included studies had a low risk of bias and nearly all original data could be retained, making this the most comprehensive multicentre data set currently available.

Considering the negative relationship between CALI and postoperative morbidity, it is advised to adapt surgical management when CALI is diagnosed. Moreover, with decreased chemotherapy responsiveness[28,61], shortened overall survival[62] and increasing doubts about the usefulness of neoadjuvant chemotherapy in certain patient groups[63], it could even be speculated that some patients would benefit from immediate resection instead of neoadjuvant chemotherapy. Prospective registration such as the ALPPS (Associated Liver Partition and Portal vein Ligation for Staged hepatectomy) Registry[64] provides a way to obtain a higher level of evidence on this topic.

Collaborators

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Supporting information

Additional supporting information may be found in the online version of this article:

Appendix S1 Study protocol (Word document)

Table S1 Search strategy (Word document)

Table S2 Inclusion criteria (Word document)

Table S3 Variables in multiple imputations (Word document)

Table S4 Quality in Prognostic Studies detailed risk-of-bias assessment of individual included studies (Word document)

Table S5 Relationship between non-alcoholic fatty liver disease activity score and lobular inflammation (Word document)

Table S6 Influence of liver injury on short-term postoperative outcomes (Word document)

Table S7 Factors related to liver injury (Word document)

Fig. S1 Flow chart summarizing final inclusion process (Word document)